Immune-mediated diseases in dogs: treatment approaches

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Immune-mediated diseases most commonly treated in dogs in practice include autoimmune haemolytic anaemia (AIHA), immune-mediated thrombocytopaenia (IMT), immune-mediated polyarthritis (IMP), polymyositis, myasthenia gravis, inflammatory bowel disease, immune-mediated skin disease, granulomatous meningoencephalitis (GME) and steroid-responsive meningoencephalitis (Figure 1**).**

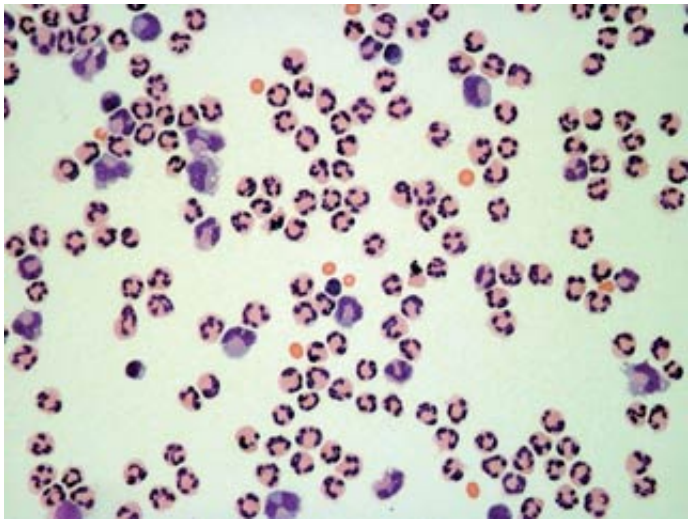

Figure 1. Cytology of CSF fluid in a dog with steroid responsive meningoencephalitis. Image: Kostas Papasouliotis, University of Bristol.

The most common and most serious of these is AIHA (**Figures 2 and 3**), which is the leading cause of mortality due to autoimmune disease in dogs – around 70% of these cases are idiopathic.

Prednisolone

Initial treatment for these conditions is normally based on immunosuppressive doses of prednisolone, with or without the addition of other immunosuppressive drugs such as azathioprine, cyclosporine and cyclophosphamide.

Substantial evidence is available that tapering immunosuppressive therapy too rapidly or too soon increases the probability of a disease relapse, often with more severe signs necessitating the re-institution of treatment at higher doses, increasing the side effects and the total treatment time.

For prednisolone, therefore, initial drug doses should be immunosuppressive and at the higher end of the therapeutic range (2mg/kg/day to 4mg/ kg/day). One recommended regime is to maintain this dose until all signs of disease are absent. Once the disease is in remission for two to four weeks, the dose can be reduced by 25% to 50% for a further month. If complete remission is maintained at the end of this month, the dose should again be reduced by 25% to 50%. This is continued monthly until a maintenance dose of 0.5mg/kg every other day is reached, and this is continued until a total of six months of treatment has been given. Therapy can then be cautiously discontinued or tapered to see if it is required at all.

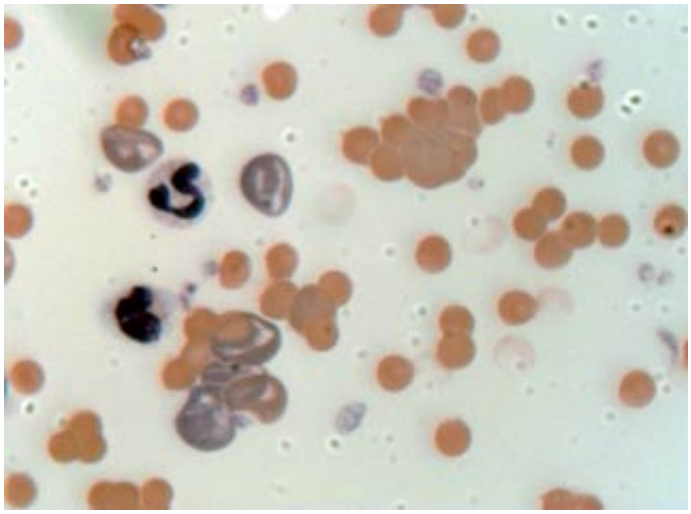

Figure 2. Blood smear in a dog with AIHA showing regenerative anaemia, polychromasia and agglutination. Image: Kostas Papasouliotis, University of Bristol.

This regime can cause marked side effects, especially in the early weeks of treatment – when the dose is high – but these normally subside as the dose decreases. Many cases can maintain remission without drugs if the therapy is tapered slowly enough. Failure to achieve complete remission within two weeks should warrant further investigation of possible underlying disease, and consideration of additional immunosuppressive treatment.

The decision whether to initially provide prednisolone alone, or in combination with other immunosuppressive drugs, is often based on the severity of the disease, concurrent illnesses and the likelihood of the dog developing severe side effects with corticosteroids. It has been shown

that, for treatment of AIHA, dogs treated from the onset with a combination of prednisolone and azathioprine have the longest survival and fewer long-term glucocorticoid complications, due to a more rapid tapering of dose compared to those treated with prednisolone alone, or in combination with other immunosuppressive drugs[1].

Alternatively, other immunosuppressant drugs can be added later if remission is not achieved, if signs relapse or if undesirable glucocorticoid side effects develop.

Azathioprine

Since azathioprine has a greater activity on delayed cellular immunity than on humoral response, it may take from one to six weeks to achieve a clinical response. The initial dose is 2mg/kg once daily for two to three weeks, reducing to 2mg/ kg every other day if remission has been achieved. For large dogs (**Figure 4**) more than 35kg, the dose should be calculated based on 50mg/m^2 once daily, reducing to 50mg/m^2 every other day after two to three weeks Calculating dosages in mg/ m^2 for dogs more than 35kg provides a more accurate reading.

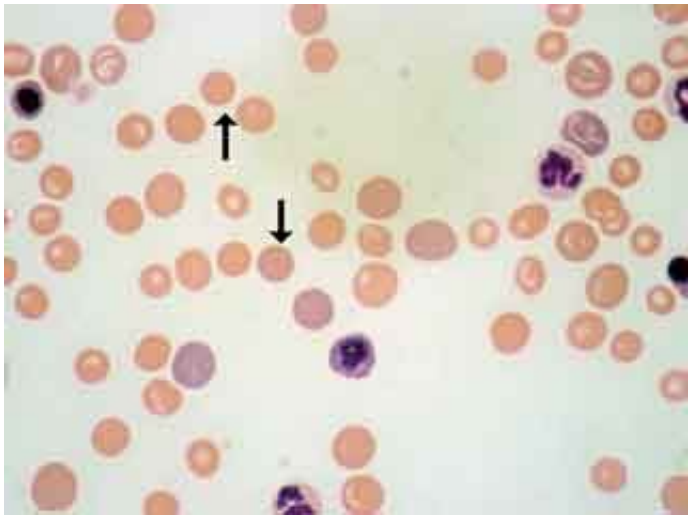

Figure 3. Blood smear in a dog with AIHA showing regenerative anaemia, polychromasia, nucleated red blood cells and spherocytes (indicated by arrows). Image: Kostas Papasouliotis, University of Bristol

No fixed regimes exist for when and how the dose of azothioprine should be tapered, but, generally, if there is still apparent remission after a further six weeks, the dose can be reduced by 50% and given on alternate days to the prednisolone. The dose can then be reduced by 50% every four to six weeks, if stable, until completely weaned off. Some cases may need to be maintained on 0.5mg/kg to 1.0mg/kg every other day for six to eight months to maintain remission before treatment can be gradually withdrawn.

The main side effects in dogs are hepatotoxicity, bone marrow suppression and necrotising pancreatitis. Hepatotoxicity is reported to occur in one in 50 dogs during the first month of treatment. This is reversible if stopped as soon as it is identified, and if it develops, treatment should not be restarted.

Bone marrow suppression is very unusual with azothioprine, but haematology should be checked every two weeks for two months, and then every one to two months. Treatment should be ceased immediately if neutropaenia or thrombocytopaenia develop. On rare occasions, an irreversible pancytopaenia can develop if treatment is not stopped fast enough. Fortunately, necrotising pancreatitis is a very rare reported side effect of this drug. Poor hair growth and gastrointestinal side effects are also infrequently seen with azathioprine.

Cyclosporine

Cyclosporine works by suppressing cell-mediated immunity and T-cell-dependent B-cell antibody production. As the drug's action is specific for lymphocytes, myelosuppression does not occur. Drug absorption is variable, and since it is metabolised by the liver, liver dysfunction or drugs metabolised by the cytochrome p450 system (such as phenobarbitone or cimetidine), it can, therefore, affect blood levels dramatically. Trough levels should, therefore, be measured 48 hours after starting treatment, and then every few weeks, and should ideally be between 300ng/ml to 600ng/ml.

Cyclosporine's onset of action is thought to be faster than azothioprine, as therapeutic levels are usually achieved in 48 hours, but there are no published studies showing whether animals receiving this drug do better with immune-mediated disease than on prednisolone alone. The starting dose rate is 5mg/ kg twice daily, reducing to 5mg/ kg once daily after approximately four weeks if still in remission, with the dose tapering every four weeks by 50% if stable.

Figure 4. When using azathioprine for AIHA, the dosage needs to be recalculated for dogs

weighing more than 35kg. Image: © istockphoto/Lukáš Hejtman.

The main side effects are anorexia, vomiting and diarrhoea. The drug's cost and the need for regular monitoring make cyclosporine an expensive treatment option, but it should be considered as an alternative to azathioprine where there is bone marrow dysfunction, if a rapid response is needed or where azathioprine has previously caused undesirable side effects. With severe immunemediated disease, a combination of prednisolone, azothioprine and cyclosporine has been advocated, although care needs to be given with such intense immunosuppression that sepsis does not result.

Cyclophosphamide

Cyclophosphamide is less widely used due to the potential side effects of myelosuppression, gastrointestinal disturbances and haemorrhagic cystitis.

With AIHA, retrospective studies have reported that combined cyclophosphamide and prednisolone was no more effective than prednisolone alone. In fact, some studies have found that the use of cyclophosphamide is associated with a poorer prognosis, with a higher mortality and morbidity rate[2,3]. The dose is usually 1.0mg/kg to 2mg/kg or 50mg/ m^2 once daily for four days/ week for four weeks, and haematology should be monitored for neutropaenia.

Leflunomide

Leflunomide is an isoxazole immunomodulatory agent that has demonstrated prophylactic and therapeutic effects in autoimmune disease in animals. In addition, it has been shown to exhibit anti-inflammatory, weak analgesic and antipyretic activity.

A retrospective study showed, in cases of cytologically confirmed immune-mediated polyarthropathy (**Figure 5**), eight out of 14 dogs showed a complete response to treatment with leflunomide, five showed a partial response and one showed a minimal response.

Adverse effects were not reported in this study, and it was considered an effective and safe alternative to prednisolone in these cases[4]. The doses used were 2mg/kg to 4mg/kg once daily, with a therapeutic trough level of 20µg/ml.

Unfortunately, leflunomide is an expensive drug, although it may be cheaper than cyclosporine.

It is recommended that dose adjustments should not be made for at least six weeks and should be based on clinical response and, ideally, cytological evaluation of synovial fluid. Haematology should be checked periodically, as leflunomide rarely causes thrombocytopaenia and leukopaenia. Elevations in alanine aminotransferase levels are also rarely seen and should be monitored.

Mycophenolate

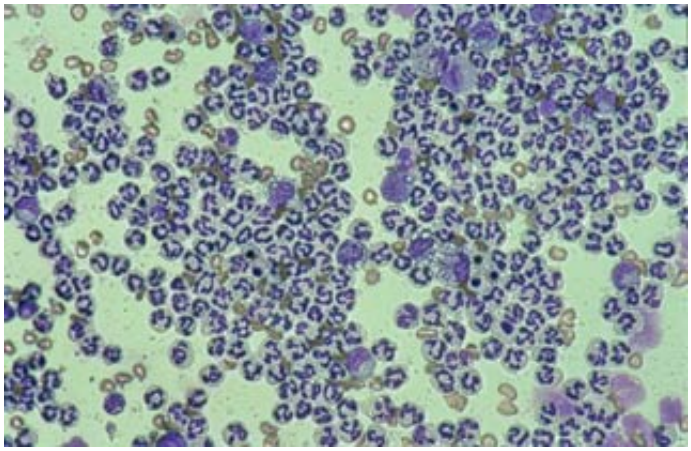

Figure 5. Cytology of synovial fluid in a dog with immune-mediated polyarthritis. Image: Kostas Papasouliotis, University of Bristol.

Mycophenolate is an immunosuppressive drug used for immunosuppression in humans undergoing bone marrow transplants, and in some with autoimmune disease, including IMHA.

The mechanism of action is very similar to azathioprine, which is to competitively inhibit purine synthesis with relative specificity for B and T-cell lymphocytes. It is much more potent than azathioprine, with less myelotoxicity and hepatoxicity, and has a more rapid onset of action than cyclosporine. Studies in dogs have shown it to be effective in experimental transplantation, and as an adjuvant treatment for canine pemphigus and myasthenia gravis.

An abstract at 2005's European College of Veterinary Internal Medicine congress[5] reported the use of mycophenolate and prednisolone in eight dogs with IMHA. Seven responded to treatment within one month, the eighth responding when changed to cyclosporine. This suggested mycophenolate was safe and effective in the treatment of AIHA in dogs. Studies of larger dog populations are required to fully evaluate its use in dogs with IMHA, but it seems a promising new alternative to other treatment regimes.

In severe or acute cases of myasthenia gravis with megaoesophagus that do not respond to pyridostigmine alone, mycophenolate has been shown to be an effective rescue treatment. In one study[6], three dogs that failed to attain clinical remission with pyridostigmine and supportive treatment alone attained clinical remission within 48 hours of a mycophenolate infusion (15mg/ kg over four hours), and were then maintained on oral mycophenolate following resolution of regurgitation.

In these cases, prednisolone is often contraindicated due to increased immunosuppression, increasing the chance or severity of concurrent inhalational pneumonia, and also due to the

increased tendency for neuromuscular weakness.

As it is relatively T-cell-specific, mycophenolate is much less likely to cause generalised immunosuppression. Reported dose rates are 20mg/kg intravenously or orally every 12 hours for three to four weeks, reducing to 10mg/kg twice daily. However, it is moderately expensive.

GME

GME is considered an autoimmune disease involving T-cellmediated delayed type hypersensitivity. Corticosteroids are considered the cornerstone of treatment. In cases that fail to respond cytosine, arabinoside (cytarabine) appears to be highly effective when used in conjunction with prednisolone. Some clinicians prefer to use cytarabine in conjunction with prednisolone from the onset in cases of GME, but there is currently no evidence for or against this practice. The recommended dose is 50mg/m^2 subcutanously every 12 hours for four injections, repeated every three weeks.

The prednisolone dose can be slowly tapered off over about six months, and the cytarabine repeated if remission cannot be maintained with prednisolone alone. The interval of the injections can be gradually increased until no longer required. However, some dogs require lifelong treatment.

Cytarabine side effects are rare and include gastrointestinal signs, hepatotoxcity and myelosuppression. A haematology should ideally be carried out a week after each treatment cycle to check for neutropaenia. Drugs used as alternatives to cytarabine include lomustine, cyclosporine, procarbazine and leflunamide.

• Some of the drugs mentioned in this article are not licensed for use in cats and dogs.

References

1. Weinkle T K et al (2005). Evaluation of prognostic factors, survival rates and treatment protocols for immune-mediated haemolytic anaemia in dogs: 151 cases (1993-2002), *J Am Vet Med Assoc* **226**(1): 1,869-1,880.
2. Mason N, Duval D, Shafer F S and Giger U (2003). Cyclophosphamide exerts no beneficial effect over prednisolone alone in the initial treatment of acute immune-mediated anaemia in dogs: a randomized controlled clinical trial, *J Vet Intern Med* **17**(2): 206-212.
3. Grundy S A and Barton C (2001). Influence of drug treatment on survival of dogs with immune-mediated haemolytic anaemia: 88 cases (1989-1999), *JAVMA* **218**(4): 543-546.
4. Colopy S A, Baker T A and Muir P (2010). Efficacy of leflunomide for treatment of immune-mediated polyarthritis in dogs: 14 cases (2006-2008), *JAVMA* **236**(3): 312-318.

5. Nielson L, Nielson S, Ramsay M and Ramsay I K (2005). *Proceedings of 15th ECVIM-CA congress*.
6. Abelson L et al (2009). Use of mycophenolate mofetil as a rescue agent in the treatment of severe generalized myasthenia gravis in three dogs, *J Vet Emerg Crit Care* **19**: 369-374.